questions that here confront us a clear recognition that solutions are chemical in nature will be of greatest service.

Louis Kahlenberg

ON THE NATURE OF RESPONSE TO CHEMICAL STIMULATION[1]

In its last analysis we may readily enough suppose that the response of organisms to any stimulus is indirectly, at least, a result of chemical stimulation. That is to say, we may suppose that any change of environmental or internal conditions, whether it be of a chemical nature or of what is ordinarily called a strictly physical nature, awakens response by reason of chemical changes which are induced by its action, and these chemical changes are themselves the starting point for the chain of reactions which eventually evince themselves as the response.

A factor like increase of temperature very likely depends for its effect considerably, if not very largely, upon the chemical readjustments which it causes within the protoplasm. We have of course in the first place what might be called the primary or unmodified effect of increased temperature—the general acceleration of chemical processes which under such conditions is axiomatic in both inorganic and organic reactions and which does not necessarily imply any change in the chemical constitution of the protoplasm. But we should not assume too readily that the case is as simple as this, for organisms do not respond in the manner in which they would were their protoplasm a stable compound. In short, we are justified in supposing that certain changes of a more or less profound nature, due to altered chemical constitution, are the net result of rise in temperature. For instance, a change of temperature will increase the intracellular activity of the protoplasm and may readily disturb the balance of the metabolic processes so that the production of a larger amount of excreted waste products will further accentuate or perhaps even modify the response by reason of a purely chemical stimulation caused by these very waste substances. Again, it is well known that one of the critical points of protoplasm as regards temperature—the coagulation point—depends upon the amount of water held by the protoplasm, including without doubt chemical as well as physical constitution of water. The less water, the higher the coagulation point, or in other words, the less water the less readily the final chemical reaction of protoplasm to heat takes place. The longer the organism is subjected to new conditions of temperature the more permanent the changes become, as is shown by the phenomena of acclimatization; and the more gradual these changes are, the less likely are they to result in the destruction of the plant.

In the response of protoplasm to light we have another instance where an external physical factor affects the chemical structure within the organism and thereby sets up reactions which are traceable to chemical stimuli. Without referring to the action of the red-orange rays in photosynthesis, I may call your attention in this regard to the action of light as a whole as a formative stimulus in tissue differentiation. In the absence of light, as is now well known, the production of the more elaborate prosenchymatic tissues is, to a large extent, if not wholly, inhibited. Now we can not suppose that light rays alone are directly responsible for, let us say, the lignification of the mechanical tissue in a stem, but their action is to cause certain chemical changes which constitute the stimulus which enables the living tissue to

[1] Address of the vice-president and chairman of Section G—Botany. American Association for the Advancement of Science, Boston, 1909.

build up this particular form of cell wall. It is interesting too to note in this connection that certain poisons of a purely chemical nature have the same effect in retarding tissue differentiation as does the absence of light. This would seem to indicate that this particular phase, at least, of the response was due to a form of auto-intoxication of the normally illuminated tissues when grown in the absence of light.

It is, however, not necessary to dwell further on this aspect of the question. Few, if any, physiologists would to-day be inclined to deny the ultimate chemical nature of the response of protoplasm to any form of stimulus. It is the purpose here to limit the examination of chemical irritation more especially to actual concrete chemical substances brought into relation with living protoplasm, and to inquire somewhat more particularly into their mode of action and the nature of the changes which they induce. The importance and fundamental nature of these reactions can not be doubted.

For this purpose we may include in the list all those substances which it may reasonably be believed induce, by their chemical action, constitutional changes in protoplasm. These substances may be mineral salts, organic compounds of great diversity of structure, including anesthetics which have been perhaps wrongly placed in a special class, and even gases of a simple constitution. They may be crystalloidal, electrolytes or non-electrolytes, or perhaps even colloidal.

As a starting point it is necessary to admit that there are certain chemical elements which must be supplied to the plant for what is considered its normal development. Ordinarily these elements are supplied to the autotrophic plant in the form of oxygen, carbon dioxide, water and solutions of certain mineral salts, with the substitution in the case of heterotrophic forms of some suitable organic compound of carbon. For all of these necessary simple substances there is supposedly an optimum tonic point of concentration, though experience shows that it may vary somewhat, and the same is true of the more complex organic food supplied to the plant devoid of chlorophyll.

Moreover, not only must these substances be presented in an acceptable form and in the proper concentration, but there must also be a proper physiological balance in the mixture of the raw foodstuffs. The relation of the plant to the so-called normal food supply is not the question which it is here specifically our purpose to discuss, and we may assume that the plant is supplied, under the most favorable conditions, with sources of raw food material and is under the influence of favorable external conditions.

However, there are some points in regard to the normal food supply which have a direct bearing upon the question of chemical stimulation, as defined even in its restricted sense, which should be referred to before passing on to the main subject. In the case of some of the necessary food materials the concentration may vary within relatively wide limits before the effects of a lack or excess of these substances are observable. In such cases the increase necessary to produce a reaction may readily be so great as to involve a material increment in the isotonic coefficient of the solution and thus confuse any result produced by any direct chemical stimulus with those initiated by the change in osmotic pressure. Potassium salts, for example, will fail to elicit any response in the growth of fungi until the concentration is so increased as to raise the osmotic pressure by several atmospheres. It is known, however, that some of the necessary salts which are required by the plant in relatively

small quantities may, if the concentration be raised above the normal point, cause a secondary stimulation of growth and eventually, if the increase be continued, become inhibitory after the manner of poisons. Iron salts accelerate the growth of certain fungi far above the normal, when present in even slight excess, although the increase in concentration is nowhere nearly sufficient to raise measurably the osmotic coefficient of the solution. It has likewise been shown that under certain conditions calcium and magnesium salts seem to stimulate growth in a manner which may be considered strictly chemical, although with some plants the added concentration makes necessary a consideration of possible osmotic changes. It should also be said that in the case of the relation of calcium and magnesium the question of physiological balance between the two appears to be especially important, though this of course would not apply to fungi where magnesium alone is required. The question of the rôle of the elements which are needed in only very small quantities, especially in the case of iron, is a highly interesting one and it is strongly suggested that they are in their normal relation to the protoplasm of the nature of chemical stimulants rather than of necessary food elements. Calcium would not indeed come under this head if, as some believe, certain calceo-proteids are essential constituents of the living substance, but for iron and to a lesser extent magnesium and perhaps even potassium a purely chemical relation is highly likely. Iron salts at least may simulate the action of a catalytic agent, a point of view which will be more fully explained later.

In any event, in speaking of necessary raw food material, the question must be regarded as a purely relative one, and one should not cling too closely to the conventional idea of what a plant must be provided with. A multitude of special cases show that the relation of protoplasm to the so-called necessary elements may be very different in different cases. Anaerobic bacteria, for instance, are exceedingly sensitive to free oxygen, the presence of infinitesimal quantities of which in the case of certain Spirilla acts as a stimulus to induce a vigorous negative tactic response. Again, among the nitrifying bacteria forms are known where the presence of sugar, usually so acceptable to non-chlorophyllous plants, acts unfavorably. Instances of this sort might be multiplied, but it is the purpose at this time simply to call attention to the fact that chemical stimulation and eventually even toxic action may result from the presence of substances ordinarily regarded as necessary to sustain life.

It is indeed the case, then, that any substance whose presence may influence the behavior of a plant either normally or abnormally is of the nature of a chemical stimulus and therefore belongs to the topic under discussion. Since, however, our knowledge along these lines is very scanty and since we can from ocular evidence recognize what may be fairly termed a normal growth in a plant, I prefer to assume for the time, as has already been stated, that a plant furnished with the necessary food materials to produce its typical morphological development and with these substances in optimum concentration, is in a state of equilibrium as far as chemical stimulation in its restricted sense is concerned.

In this connection attention may be called to what appears to be an error in the point of departure of some investigators who have endeavored to determine the relative stimulatory value of certain substances, whether these be necessary or not to the plant. The mistake comes in the reference to distilled water as the medium

in which control cultures are grown, the variant being the same distilled water plus the substance under investigation. It is obvious that metabolic processes and consequently growth can take place only in such plants or plant parts in which elaborated food material is stored. It is equally obvious that the osmotic relations must be disturbed. Besides the lack of chemical balance there is also a lack of physiological balance. Plants under experimentation to determine the effect of chemical stimulation should be referred for comparison to those grown under conditions which are as nearly as may be the ones which can be recognized as producing opportunity for what experience shows is the natural morphological development of the organism. The physiologist should no more neglect the morphological aspects of his investigations than should the morphologist the physiological.

In its restricted sense, then, chemical stimulation may be said to deal with the effects of chemical agents which are not only not necessary, but which may be positively deleterious to the organism—poisons in short. It has been established that many, if not all, classes of substances which exert a toxic action on protoplasm will become stimulatory if presented to the cells in sufficiently small doses. Somewhere between an infinitesimally weak solution which produces no reaction, to the toxic dose which kills there is a stimulative optimum which gives the maximum of reaction. Experience shows that this is true of widely different substances—a poisonous gas like carbon monoxide, a poisonous metallic salt like copper sulphate, a simple organic compound like chloroform or a more complex one like an alkaloid, all come under this head. The question which concerns this paper is not the possible ultimate lethal effect of these poisons, but how far they may serve to excite the protoplasm to extraordinary activity. The amount required to effect the latter result will naturally vary with the substance, certain mild poisons possibly never affecting the plant beyond the stage of stimulating growth, no matter how high a concentration was employed.

From the work of Raulin and others, it is known that metallic salts in themselves toxic to protoplasm will, if presented to it in minimal doses, accelerate vegetative processes in a variety of plant forms. Certain fungi may be made to develop their vegetative hyphæ much more luxuriantly by the addition to their nutrient substratum of quantities as small as .0005 normal of zinc sulphate, and the increase of dry weight of cell substance produced may exceed by 200 per cent. or more that which is formed by similar cultures without stimulation. Nor is this limited to salts of the heavy metals, nor indeed to inorganic substances, for organic substances such as glucosides and alkaloids, or even simpler ones like chloroform, produce a similar if not so marked result.

In the concentration necessary to produce the characteristic reactions there is great diversity. As would be expected, not only are different substances very unequally stimulatory or toxic, but also the same substance varies greatly in the amount required to stimulate different organisms. Copper sulphate, one of the most violent of poisons to plant protoplasm, does not inhibit the growth of *Penicillium* until a concentration of nine per cent. is reached, yet the effect of the same salt is so enormously poisonous to many algæ that an infinitesimally weak solution will speedily cause death. What is true of the toxic point is true also of the stimulatory optimum. In the attempt to explain such disparities stress has been laid by some on

the probable impermeability of the cell membranes to this highly toxic salt in the case of the resistant forms. I am inclined to believe myself, however, that it is probably not so much due to such causes as to specific differences in the constitution of the protoplasm itself, which renders the usually poisonous substances relatively inoperative. There hardly seems enough evidence to support the idea of any very highly specialized qualitative selective power on the part of the cell membranes in the matter of dissociable and diffusible salts. On the other hand, there are many reasons for looking upon protoplasm not as a uniform substance, but as differing considerably in different plants. The fact that some plants can not thrive except in the complete absence of oxygen is enough to illustrate this point. The condition of the stimulated plant may itself cause a variation in the optimum concentration of the stimulant, as is shown by the effect of rise in temperature on the lowering of the toxic or stimulatory dose. It is not only among lowly organized plants like fungi that stimulation follows such conditions, but among the higher vascular plants as well. We can not suppose that these stimulants react directly upon the protoplasm or themselves supply the energy necessary for the changes which they induce with a possible reservation in the cases of those salts whose valency may be subject to change. In the first place, they fall in very different groups of toxic substances, if we take Loew's well-known classification, and yet there is a great similarity in the reaction produced. Therefore it is reasonable, for the time being, to disregard to a considerable extent the question of the chemical nature of the stimulating substance as far as its effects in accelerating the life processes of the organism are concerned. This does not mean, however, that the ultimate effect on the manner in which these poisonous substances may, in strong solutions, kill the protoplasm is not related to the chemical nature of the toxic agent. Not only are the stimulants not the sources of energy for the changes involved, but also they can not, in most cases at least, be regarded in themselves as catalyzers, no matter how greatly the end result of their action might suggest their being of such a nature. If, therefore, we are to find any satisfactory clue to the answer to the question of the influence of these minute doses, we must look rather towards the indirect effect they may exert and endeavor to discover if they may not encourage the formation by the protoplasm itself of substances which do act in a catalytic fashion. It seems clear, then, that the poisonous action of a given substance may be, and probably commonly is, very different from the stimulating effect of small doses of the same substance.

Whether it is safe to say that all substances which are toxic must of necessity act as stimulants if presented in sufficiently dilute form is a question. It is conceivable that some might produce no reaction unless present in a lethal dose, but it seems probable that most substances will show a stimulating reaction at the proper dilution. In this connection it is well to remember that we should not confuse the necessarily more complicated reaction of higher animal forms, whose balance of function is so delicate and whose tissue structures are so very diverse, with the more fundamental and presumably simpler and more direct reactions of the less interdependent cell aggregations such as are found in plants. It is reasonable to suppose, however, that as far as the cells themselves are concerned the underlying principles are much the same in all organisms.

Upon inquiring more closely into the effects of stimulants, we find that while a

great deal is unknown there are a number of important facts concerning which there is positive information and which throw considerable light on what is really taking place under such conditions. It is best, before taking up the physiological reactions, to consider the morphological changes which ensue, which, if we wish to employ modern terminology, we may term "chemomorphosis." The information regarding the lower forms—particularly the fungi—is the fullest and will be considered first.

The primal fact of the increase on dry weight has already been spoken of and is the simplest of all the reactions to demonstrate. By the easy process of the desiccation and weighing of a series of cultures the stimulation curve of the whole range of possible concentrations from minimum to maximum may be determined. Although it must be said that to obtain definite results means which might seem to some to be exaggeratedly careful must be taken to ensure the purity of all substances entering into the culture medium. Not only is the quantity of mycelium formed greater, but also the form and appearance are very different. Fungi commonly cease to form conidia under stimulation, the mycelial felts are buckled and knotted instead of being flat and even and their consistency is different, being tough and leathery instead of somewhat tenuous in texture as in the normal growth. In short they present every appearance of more luxuriant vegetative activity. The cell forms are often different, especially among bacteria, where the so-called involution forms arise apparently from chemical stimulation. Among many of the fungi, at least, such conditions are tantamount to a state of hyperplasia, if we may use the term in speaking of such lowly organized forms. Among the higher plants there may be simply an increased rate of growth and an ultimately greater stature, or, in other cases, as in the local application of metallic salts in initiating local intumescences or in hastening and increasing the formation of wound tissue, actual hypertrophies may be induced. In the stimulation afforded by parasitic fungi or by gall insects the great expression of abnormal growth is to be seen amounting often to relatively large outgrowths of tissue. The reaction in these various cases would seem to differ rather in degree than in kind, and it is perhaps a question not in this case of a mere hastening of growth, but of the excitation being sufficiently violent to destroy the equilibrium of growth which exists among the cells.

In no such case, however, have we any evidence that the variations in form so induced are inheritable. It is only when the germ cells at or near the time of their formation are directly stimulated that we get any changes in the offspring which are passed on to the succeeding generations. Sometime, it may be, means will be found by which an excitation of the sporophyte can be made in some way to influence the gametophytic cells and thus induce permanent variations through influences brought to bear indirectly upon the gametophyte, though it is not to be supposed even in that case that the particular response induced in the original sporophyte will be repeated in its offspring.

It is evident, from the effect of parasitic fungi upon their hosts, that not only does the stimulus of the parasitism of a specific fungus produce more or less specific results, but also that the condition of the parasitized cells themselves influence the result. The more primitive or meristematic are the cells the greater the resultant effect in the way of a distortion, for, as is well known, the greatest hypertrophies take place when the infection is in the

growing points of the shoots and becomes less and less when the more stable and permanent tissues like leaf parenchyma are attacked. The same fungus which causes real hyperplasia in young tissue produces but a hypertrophic enlargement in the adult parenchyma.

Such being the case, one might be warranted in reasoning by analogy that the still more plastic cells of the gametophyte would be even more profoundly influenced by stimulation and such indeed appears from MacDougal's experiments to be the case. It is also not unreasonable to suppose that the inciting cause of the healing of wounds, of stimulus to growth after injury, and even of regeneration phenomena themselves, harks back to a question of chemical stimulation. In the more massive tissues, at any rate, wounding results in the exposure of interior cells directly to the action of the oxygen of the air, and is accompanied by increased metabolic activity. The more rapid growth of injured parts, the awakening of dormant buds, may well be influenced or initiated, though probably not eventually controlled, by chemical stimulation arising from this or similar causes.

It is not to be supposed in any case that the chemical substances in question themselves constitute—by any direct union with the protoplasm—the modifications which ensue. It is only possible here to touch thus briefly upon the morphological responses induced by chemical stimulation, for the field is an enormous one. In some of its aspects, the study of the immediate effect of environment upon the external and internal form of a plant comes under this head. There is without question a large and inviting field for investigations into the nature of the changes in structure which are correlated with chemical stimulation.

It is necessary also to pass over without further comment the directive effects of chemical stimulation upon growth and movement, concerning which there are many investigations as to the expression of the reaction, but very little information as to the intimate causes of it.

After this brief consideration of the changes in the actual amount of elaborated substance, of stature and of structure which commonly attend chemical stimulus and which are the outward signs of its workings, we may next turn to the more fundamental question of what we know of the influence of this excitation on the physiological activities of the plant.

One fact which is clearly marked in the case of certain fungi that have been investigated is that the protoplasm, when stimulated, works more economically in respect to the carbohydrate food material supplied than when unstimulated. The latter produces a larger crop, as estimated from the dry weight, from a given amount of sugar than the normal culture does: there is less waste. Were the metabolic activity of protoplasm to be interpreted simply in terms of economy of action, one might be tempted to speak of such a condition as more nearly approximating a perfect or so-called normal; but when we reflect that we know so little of the chemical action and interaction of living protoplasm, it would be unwarranted to assume that mere economy of consumption of one form of food material would tell the whole story. The plant is attuned to an average condition and its attunement to that condition constitutes the nearest approach to what we may call normal. The increased availability of the sugar under chemical stimulation may be regarded as an untoward, fortuitous condition which, while it may be optimal for the processes involved in building up vegetative hyphæ, is not optimal for the development of the

plant as a whole, as is evidenced by the suspension of spore formation. This increased availability of the carbohydrate food is, then, distinctly unusual as far as the ordinary life processes of the fungus are concerned. The cessation of conidial spore formation which characterizes even slight stimulation is a morphological abnormality in the usual life cycle of the mostly asexual hyphomycetous fungi, and while it might be argued that spore formation is an evidence in itself of at least the initiation of unfavorable conditions, such considerations hardly apply here. It would be true only in a very limited degree, for the stimulus to spore formation need not necessarily be inimical in any large sense of the word. Whether it is the more economical working of the protoplasm which inhibits the formation of conidia or whether the absence of the latter results in less waste of energy in metabolism is perhaps a question, though probably most would agree that the spore-forming process is one that demands a greater expenditure of energy than the mere vegetative growth of the hyphæ.

From what we know of the effect of chemical stimulants upon the eggs of organisms, it would look as though the processes set up by such excitation are more critical for the sexual cells than for those of what may be regarded as the sporophyte. It would be exceedingly valuable to discover more about the relation of chemical stimulation to the production of gametes or their equivalents, and here we have another attractive field that has not been largely cultivated. It may be said in passing that as far as these non-sexual hyphomycetous forms are concerned there is not much evidence to show that such chemical stimulation as has been tried is sufficient to restore the ability, in many cases long lost, to produce sexual fruit.

It has been stated that there is less waste as well as a greater economy in manufacture of dry substance. One would naturally suppose that the two go hand in hand, but it is well to specify more definitely in what this smaller waste consists. One of the characteristic products, though not indeed necessarily an end product of katabolic activity in the plant cell, is oxalic acid, particularly in the case of these same fungi which we have been considering, where it is freely excreted into the substratum. Now the amount of this may be determined with relative ease, and it has been shown that with a stimulated crop there is a marked decrease in the ratio of the oxalic acid formed to the amount of dry substance produced in a given time. Together with this the carbon dioxide production does not appear to much more than parallel the increase in the weight; or in other words, the formation of this gas is approximately normal. This being the case, it at once becomes evident that the carbohydrate represented by the difference of oxalic-acid production in the normal and in the stimulated plants is at the disposal of the organism in the constructive processes. As for the higher plants, it has been shown that an increase in carbon-dioxide production takes place under stimulation, but these results are hardly complete, having been made without reference to net gain in substance. This matter should be further investigated, since it appears that the formation of wound tissue, when subjected to stimulation, is accompanied on the average by a greatly lessened carbon-dioxide production as compared with unstimulated growth; and this, too, in spite of the fact that there is ocular evidence that greater cell activity results under conditions of stimulation.

A highly interesting and instructive light on this question is thrown by the be-

havior of *Sterigmatocystis nigra* in relation to its assimilation of nitrogenous material. This fungus has the power, to a limited extent at least, of assimilating free nitrogen from the air. Stimulation appears to diminish this ability and to cause the fungus to rely more largely upon the nitrate fed to it: or at any rate the organism does not excrete into the liquid substratum as large an amount of waste nitrogenous products as does the normal. Furthermore, the nitrogenous content of the dry substance of the plant is not affected one way or the other. In regard to the nitrogen supplied in combined form, there is less thrift in the stimulated than in the normal growth, but, on the other hand, the total amount of nitrogen involved, including that excreted as waste into the substratum, is less in the former than in the latter case. This whole question is, of course, a hugely complicated one and in the light of our relatively slight knowledge of nitrogen metabolism one which should be approached with caution. But it is evident that the problem is of great importance.

In this connection it is apropos to quote from practically the only investigation we have which touches on this point.

> To explain the reason for the activity of the organism along these lines there are these suggestions: one that the fixation of free nitrogen and its excretion in combined form may be a function connected with fructification, since stimulated felts do not produce spores; another . . . is that the stimulated crop, driven to its most rapid metabolic activity by the stimulant, is forced to consume its carbohydrate more economically and therefore finds less energy to use in effecting the combination of the relatively inert and difficultly combinable nitrogen, and so must use the more readily assimilable compound nitrogen; or again it may be that since by the presence of the stimulant the fungus can consume carbohydrate more thoroughly and with less waste, therefore it finds in what would be a normal amount under ordinary circumstances a more than necessary amount under the favoring influence of the stimulant, which, of course, would be then potentially a too great supply, and the result would be over feeding in this direction and therefore there would be a tendency to lessened activity in expending energy for nitrogen combination. This last hypothesis is in accord with conclusions that have been reached on the activity of the root tubercle bacteria in fixing nitrogen when well supplied with nitrogen compounds, but not in accord with the results of those who find that the fixation of nitrogen is directly proportional to the amount of sugar at hand.

After consideration of the whole matter, one is inclined to the opinion that, after all, since less nitrogen passes through the fungus for the amount of dry substance formed, there is economy in nitrogen as well as in carbohydrate metabolism in a stimulated growth. And taking it all in all, there seems to be sufficient evidence for maintaining that under chemical excitation of optimum intensity the waste involved in mere cell formation, at least, is not so great in stimulated as in unstimulated protoplasm.

In this connection there arises at once another question of great importance, namely, what influence stimulation has on enzymatic activity. While the data on this point are still incomplete, it is permissible here to make reference to certain results not yet completed which throw some light upon this phase of the matter. Here again *Sterigmatocystis nigra* is valuable for experimentation. In common with many of its kind, this fungus can live on a great variety of substrata, its ability to do so being due in large measure to its versatility in the excreting of an enzyme appropriate to the particular compound on which it is growing. Thus it will produce maltase when grown on maltose, sucrase when grown on saccharose, inulase on inulin, amylase on starch, etc. A quantitative estimation of its hydrolyzing power

would afford some clue to the enzymatic activity of the stimulated fungus as compared with the normal growth, and experiments seem to show pretty clearly that there is greater proportional enzymatic activity in the former than in the latter. The same point is even more clearly illustrated by the various researches on the influence of chemical irritation upon alcoholic fermentation by yeasts. A variety of substances in minimal doses have been found to increase the fermentative activity of these fungi. While in such cases we are, of course, dealing with extracellular enzymes, it is not unreasonable to suppose that by analogy similar excitation follows with the intracellular enzymes. The intracellular enzymes are the ones which we may legitimately suppose to be connected more or less directly with the metabolic activity of the living organism. Now if anabolic activity is connected in any way with the reversible action of enzymes—as seems likely—we have here another link in the chain of evidence as to the real nature of chemical stimulation. We may hope in time to reduce it entirely to a question of enzyme formation. In order to do so we must devise more precise means for investigating the intracellular enzymes in the plants experimented upon and to determine if there is any quantitative difference as a result of stimulation. If it can be proved that this causes a relative increase in synthesizing enzymes in the fungus hyphæ a long step toward a more complete understanding of the processes will have been made. It should be acknowledged that at present such considerations are in a measure purely speculative, yet not speculative to the extent of being other than founded on the meager knowledge at hand. There is nothing improbable in such conclusions. The synthetic action of enzymes is a question which is more and more attracting the attention of the investigator, and while the results along these lines are comparatively new and relatively few in number, they are sufficiently conclusive to permit of a broad application of the principle involved. I will cite only one instance, and that in relation to an extracellular enzyme, where isomaltose has been synthesized from glucose by the action of maltase and, further, where the same enzyme was utilized in the synthesis of the glucoside amygdalin. Granting then that we may have in enzymes active agents in the constructive work of the organism, it is possible to understand how an increase in enzymatic activity could explain many of the phenomena connected with the response to chemical irritation.

There still remains, of course, the most fundamental question why and in what manner the specific irritants used affect the quantitative and even perhaps the qualitative formation of enzymes, and here there is no ready or sufficient answer to give. At first glance it does not appear to be connected with their dissociation in weak solutions, for non-electrolytes like morphine give a reaction as well as dissociable salts, although it is to be remarked that the concentration required with the former is many times greater than with the latter. If, as is believed by some, the *poisonous* action of salts depends on the degree of their dissociation, it is probably equally true that the stimulative action of minimal doses of these same salts is influenced by this same factor. But this assumption does not dispose of the large class of non-electrolytic poisons (and consequently stimulants), although I venture to suggest that the introduction of such substances into the sphere of protoplasmic activity may result in the formation by the protoplasm of by-products which are dissociable poisonous substances. Such an explanation would help to account for the large doses

of non-electrolytes which are necessary to produce a reaction on the plant organism.

There seems to be a much greater universality in the manner of the response to stimulation by poisons than in their actual toxic effect, a fact that has already been noticed, and for that reason I am strongly inclined to the opinion that the former does not depend upon the particular form which the latter may take, and so the increased enzymatic action may be considered to be a general phenomenon connected with this class of response.

There at once suggest themselves many very interesting problems in regard to the relation of chemical stimulation to morbid hypertrophies—using the word in its broadest sense—in higher plants, and also to what might be called the normal hypertrophies which ensue in the tissues of the ovary wall and surrounding parts after fertilization, without touching on the great question of the development of the fertilized egg itself.

In a previous address before this section, attention was called to the possible enzymatic changes induced by untoward chemical stimulation of the germ cells of certain plants and the results of this stimulation on the offspring. In the light of my own acquaintance with the question of chemical stimulation I see nothing improbable in such a point of view, even though we can not prove it at present.

There are many other considerations in connection with the question which might be profitably discussed and I am aware that I have really touched upon one side of the problem only, practically neglecting the morphogenic influence of chemical stimulants, but sufficient time has already been consumed and to open up new topics would be but to strain your patience further. The point which I have endeavored to develop and which I here repeat is that the chemical stimulants which have been discussed produce their effect indirectly and the nature of the response appears to be one of the increase of constructive enzymatic action over that which would take place under normal conditions from an equal and similar food supply.

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PUBLIC LECTURES AT THE HARVARD MEDICAL SCHOOL

The faculty of medicine of Harvard University offers a course of free public lectures, to be given at the Medical School, Longwood Avenue, Boston, Saturday evenings at 8, and Sunday afternoons at 4, beginning January 2, and ending April 30, 1910. Doors will be closed at five minutes past the hour. No tickets are required. Following is a list of the lectures and their subjects, with dates:

January 2—"The Influence of Mental and Muscular Work on Nutritive Processes" (illustrated), by Dr. F. P. Benedict.

January 8—"The Story of Vaccination," by Dr. M. J. Rosenau.

January 9—"What the Public should know about Patent Medicines," by Dr. M. V. Tyrode.

January 15—"Clean Milk" (illustrated), by Dr. Calvin G. Page.

January 16—"The Growth of School Children and its Relation to Disease," by Dr. W. T. Porter.

January 22—"Sprains, Strains and Fractures: Simple Facts of Diagnosis and Treatment" (illustrated), by Dr. J. B. Blake.

January 23—"The Glands of Internal Secretion and their Relations to Health and Disease" (illustrated), by Dr. W. B. Cannon.

January 29—"Small-pox" (illustrated), by Dr. J. H. McCollom.

January 30—"Hearing and Speech," by Dr. C. J. Blake.

February 5—"Posture and Carriage as affected by School and Clothing," by Dr. R. W. Lovett.

February 6—"The Care of Infants with Special Reference to the Prevention of Disease," by Dr. Maynard Ladd.

February 12—"Voice Production," by Dr. J. Payson Clark.